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Environmental Protection Agency

Office of Emergency and Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati OH 45268

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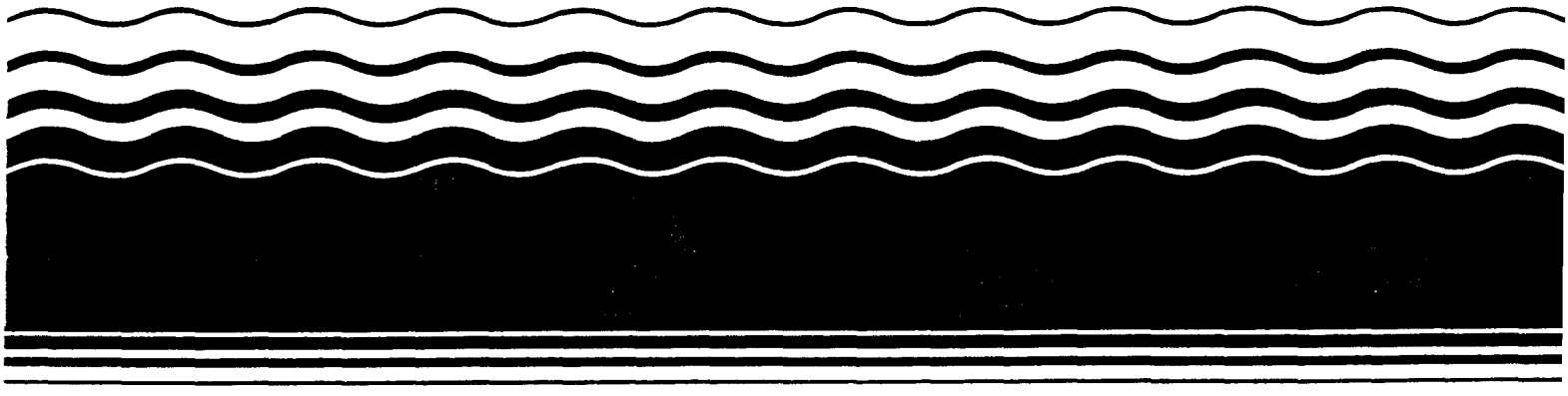
HEALTH EFFECTS ASSESSMENT FOR PENTACHLOROPHENOL



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DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with pentachlorophenol. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Pentachlorophenol. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-065. NTIS PB 81-117764.

U.S. EPA. 1985. Drinking Water Criteria Document for Pentachlorophenol. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. Final draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

There are a number of subchronic oral animal studies which agree well concerning the NOAEL for pentachlorophenol. Although fetotoxicity has been associated with pentachlorophenol exposure, the NOAEL for this endpoint appears to be in the same range as the NOAEL for liver damage in adult animals. The sole chronic study suggests the same effect level as the subchronic studies. Therefore, the estimated oral AIS and AIC are both 2.1 mg/day. A CS of 20 was derived based on fetal toxicity in rats exposed orally during the reproductive period.

There are no adequate data concerning inhalation exposure to this compound.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical abstract service
CS	Composite score
GI	Gastrointestinal
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RV_d	Dose-rating value
RV_e	Effect-rating value
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of pentachlorophenol (PCP) (CAS No. 87-86-5) are as follows:

Chemical class:	polychlorinated phenol	
Molecular weight:	266.35	
Vapor pressure at 20°C:	1.1×10^{-4} mm Hg	(Verschueren, 1983)
Water solubility at 20°C:	14 mg/ℓ	(Verschueren, 1983)
Log octanol/water partition coefficient:	5.01	(Verschueren, 1983)
BCF:	13 in sheepshead minnow, Cyprinodon variegatus	(U.S. EPA, 1980b)
Half-lives in:		
Air:	unknown	
Water:	14 days	(Boyle et al., 1980)
Soil:	48 days	(Rao and Davidson, 1982)

A half-life value for pentachlorophenol in air is not available. Assuming a first order reaction, and using the equation

$$LN \frac{A}{A-X} = R_1 \times T,$$

where:

A = initial concentration

X = concentration at time "T"

R_1 = rate constant,

photodecomposition half-lives of 2.2 days and 32 days may be calculated from the data on the irradiation of pentachlorophenol with light of wavelengths >290 nm when the compound was adsorbed on silica gel and coated on glass plates, respectively (Korte et al., 1978).

The mobility of pentachlorophenol in soil is not known with certainty. It has been reported that pentachlorophenol sorption in soils is dependent on soil pH and organic matter content. In organic-rich acidic soils, pentachlorophenol is likely to be sorbed strongly (U.S. EPA, 1985). Conversely, pentachlorophenol may leach from soils having neutral or basic pH and low organic matter content.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

The available studies indicate that pentachlorophenol is absorbed rapidly from the GI tract. Rats exposed to pentachlorophenol either in the diet (350 ppm) or in drinking water (~32 mg/ℓ as sodium pentachlorophenol) had plasma concentrations of 30±3 and 40±8 μmol/ℓ pentachlorophenol, respectively, after 7 days of exposure (Meerman et al., 1980). Braun and Sauerhoff (1976) reported that the average half-time for GI absorption of pentachlorophenol in monkeys was 2.7 hours. Braun et al. (1978) reported that the average half-time for absorption of pentachlorophenol in human volunteers was 1.3±0.4 hours, following administration of a single dose (0.1 mg/kg bw). Braun et al. (1977) also reported on the absorption of pentachlorophenol in rats. Following administration of a single oral dose of 10 mg PCP/kg bw, peak plasma levels of pentachlorophenol were reported to be 45 ppm for both males and females 8-12 hours post-treatment.

2.2. INHALATION

Casarett et al. (1969) demonstrated that pentachlorophenol is readily absorbed by inhalation. Workers exposed to pentachlorophenol in a wood-treating plant in Honolulu were found to have pentachlorophenol in their urine. In order to determine the possibility of pentachlorophenol absorption by inhalation, two workers spent 45 minutes in an enclosed process area resulting in mean urinary concentrations of pentachlorophenol equal to 230 ng/ℓ and 432 ng/ℓ for the first and second worker, respectively. Based on respiratory rates, estimated tidal volume and pentachlorophenol recovery in the urine, absorption of pentachlorophenol by these two men was estimated to be 88 and 76%, respectively, of the estimated inhaled dose.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

Epidemiological studies have revealed a variety of adverse effects due to occupational exposure to pentachlorophenol, but the routes of exposure (dermal, oral, inhalation) cannot be separated. These effects include serum enzyme induction (Klemmer, 1972), increased incidences of low-grade infections and inflammation (Klemmer et al., 1980) and depressed kidney function, which may be partially reversible (Begley et al., 1977).

3.1.1. Oral. Several studies of the subchronic oral toxicity of pentachlorophenol in experimental animals are summarized in Table 3-1. Deichmann et al. (1942) exposed rats, cats and rabbits to pentachlorophenol either in the diet or by gavage, but the purity of the pentachlorophenol was unspecified, and the number of animals observed was small. Also, a number of investigators have found that technical grade pentachlorophenol, contaminated with dibenzo-p-dioxins, produced effects in rats (following subchronic exposure) that were not seen in parallel experiments where pure pentachlorophenol was used (Johnson et al., 1973; Goldstein et al., 1977; Kerkvliet et al., 1982a,b). The remaining studies summarized in Table 3-1 used "pure" pentachlorophenol.

NOELs of 3 mg/kg bw/day and 100 ppm are derived from the rat studies of Johnson et al. (1973) and Goldstein et al. (1977), respectively. Given an average rat weight of 300 g and assuming a daily food consumption of 5% of its body weight, 100 ppm may be adjusted to 5 mg/kg bw/day.

A LOAEL of 50 ppm based on liver lesions might be established from the Kerkvliet et al. (1982a,b) study on mice (number of animals was not specified). Assuming an average food intake of 13% of the body weight/day, the 50 ppm dietary concentration may be adjusted to 6.5 mg/kg bw/day.

TABLE 3-1

Subchronic Toxicity of Orally Administered Pentachlorophenol

Species	Number	Dose	Duration	Effects	Reference
Rat	10/group	588 ppm in diet 300 ppm in diet	26 weeks 28 weeks	No gross signs of toxicity. Decreases in food consumption and body weight at both doses. Unspecified histological abnormalities.	Deichmann et al., 1942
Rat	NR	0, 3, 10 or 30 mg pure PCP/kg bw/day	90 days	Increased liver weight at 10 and 30 mg/kg. Increased kidney weight at 30 mg/kg.	Johnson et al., 1973
Rat	6/group	0, 20, 100, 500 ppm pure PCP in the diet	8 months	At 500 ppm: increased glucuronyl transferase to aryl hydrocarbon hydroxylase activities; reduction in body weight.	Goldstein et al., 1977
Mouse	NR	0, 50 or 500 pure PCP ppm in the diet	10-12 weeks	Lesions in the liver at both doses. Dose-related induction of splenic tumor development following MSV/MSB challenge.*	Kirkvliet et al., 1982a,b
Rabbit	5	35 mg/kg bw by gavage raised from 35-200 mg/kg bw	15 days at 35 mg/kg bw; 19 days after day 15 dose of 35 mg/kg bw	Death upon ingestion of a total of 190-390 mg/kg bw.	Deichmann et al., 1942
Rabbit	23	3 mg/kg bw by gavage	6 days/week for 15 weeks	No effect.	Deichmann et al., 1942
Cat	4	1.25 or 2.5 mg/kg bw	10 weeks	No effect.	Deichmann et al., 1942
Pig	4/group	0, 5, 10 or 15 mg pure PCP/kg bw/day	30 days	10 and 15 mg/kg/day: Increased liver weights. Unspecified dose: diffuse, cloudy swelling of the hepatocytes. No histopathological changes in the liver, kidney, spleen, brain and muscles. No effect on body weight or blood chemistry.	Greichus et al., 1979

*Assessment of the immune system
NR = Not reported

3.1.2. Inhalation. Pertinent data regarding subchronic inhalation exposure to pentachlorophenol could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. Only one chronic study regarding oral exposure to pentachlorophenol was located in the available literature. Schwetz et al. (1978) exposed groups of 27 male and 27 female rats to 0, 1, 3, 10 or 30 mg purified pentachlorophenol/kg bw/day for either 22 months (males) or 24 months (females). During the study, body weight, food consumption and general behavior were recorded on a monthly basis. Upon termination of the study, endpoints observed included gross and microscopic pathology, organ weights, hematological and urological variables and clinical chemistry. At the 30 mg/kg/day level of treatment, a reduced rate of body weight gain and increased specific gravity of the urine were observed in females. Furthermore, both sexes had increased SGPT enzyme activity at this level of exposure. Pigmentation of the liver and kidneys was observed in females exposed to 10 or 30 mg/kg/day, and in males exposed to 30 mg/kg/day. The 3 mg/kg bw/day level of exposure thus represents a chronic NOEL.

3.2.2. Inhalation. Pertinent data regarding chronic exposure to pentachlorophenol by inhalation could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. A number of studies that have investigated the teratogenicity of orally administered pentachlorophenol in rodents are summarized in Table 3-2 (Larsen et al., 1975; Schwetz and Gehring, 1973; Schwetz et al., 1974a,b, 1978; Hinkle, 1973). Although these studies failed to demonstrate teratogenicity, fetotoxic effects associated with delayed

TABLE 3-2

Teratogenicity of Orally Administered Pentachlorophenol

Strain/Species	No. Dams	Dose	Vehicle	Days Administered	Effects	Reference
CD rats	6/group	0 or 60 mg/kg bw	pure PCP by gavage	single dose on day 8, 9, 10, 11, 12 or 13 of gestation	Three of four malformations were seen when pentachlorophenol was administered on day 9 of gestation. Treatment on day 9 or 10 resulted in significant reduction in fetal weight gain. The authors concluded that the malformations could have resulted from maternal toxicity.	Larsen et al., 1975
Sprague-Dawley rats	NR	0-50 mg/kg bw/day	NR	daily doses on day 6-15, 11-12 or 15 of gestation	Dose-related fetotoxicity with a LOAEL at 5 mg/kg bw/day.	Schwetz and Gehring, 1973; Schwetz et al., 1974a,b
Sprague-Dawley rats	20/group	0, 3 or 30 mg/kg bw/day	diet	62 days prior to mating, throughout gestation to lactation	No effect at 0 or 3 mg/kg bw/day. 30 mg/kg bw/day: Significant reduction in neonatal body weight; decreased percent survival of pups and decreased percent live births. Increase in lumbar spurs and vertebrae with unfused centra were attributed to fetotoxicity. This dose also resulted in maternal toxicity.	Schwetz et al., 1978
Golden Syrian hamsters	NR	1.25-20 mg/kg bw/day	NR	days 5-10 of gestation	Increase in fetal deaths and/or resorptions in 3 of 6 groups tested. No other details in the abstract.	Hinkle, 1973

skeletal ossification were observed. Schwetz et al. (1974a,b) and Schwetz and Gehring (1973) reported a dose-related fetotoxicity with a LOAEL of 5 mg pentachlorophenol/kg bw/day. A NOEL of 3 mg/kg bw/day was established from the study of Schwetz et al. (1978), in which 10 male and 20 female Sprague-Dawley rats were fed pentachlorophenol 62 days prior to mating and throughout gestation and lactation. Fetotoxic effects as well as maternal toxicity were seen at a level of 30 mg pentachlorophenol/kg bw/day. Since pentachlorophenol apparently does not cross the placental barrier, the observed fetotoxicity may be a reflection of maternal toxicity (Larsen et al., 1975).

3.3.2. Inhalation. Pertinent data regarding the teratogenicity of inhaled pentachlorophenol could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

A recent study (Boberg et al., 1983) indicates that pentachlorophenol antagonizes the tumorigenic effects of either 1'-hydroxysafrole or its metabolite, 1'-sulfooxysafrole, in mouse liver. In addition, pentachlorophenol is known to reduce the toxicity of N-hydroxy-2-acetylaminofluorene (Meerman et al., 1980; Meerman and Mulder, 1981). In both cases the antagonistic effects of pentachlorophenol were reported to be due to inhibition of cytosolic sulfotransferase.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the carcinogenicity to humans of ingested pentachlorophenol could not be located in the available literature.

4.1.2. Inhalation. Pertinent data regarding the carcinogenicity to humans of inhaled pentachlorophenol could not be located in the available literature.

4.2. BIOASSAYS

The NTP (1983) is currently testing technical grade pentachlorophenol and Dowicide EC-7 (pentachlorophenol) for carcinogenic activity. However, results from these studies are not yet available.

4.2.1. Oral. Two studies demonstrated that pentachlorophenol was not carcinogenic when administered orally. Bionetics Research Laboratories (BRL, 1968) administered 46.4 mg pentachlorophenol/kg bw/day by gavage from days 7-28 postpartum to two strains [(C57B1/6 x C3H/Anf)F_1 and (C57B1/6 x AKR)F_1] of male and female mice (18/sex/strain). At 28 days postpartum, the mice were transferred to diets containing 130 ppm for 78 weeks. No significant increase in the incidence of tumors was seen in the treated animals relative to sham-treated controls (79-90 mice/sex/strain).

Schwetz et al. (1978) exposed groups of 27 male and 27 female Sprague-Dawley rats orally to 0, 1, 3, 10 or 30 mg pentachlorophenol/kg bw/day for 22-24 months. No significant increase in the numbers or types of tumors was observed in the treated animals compared with controls.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled pentachlorophenol could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Pentachlorophenol was not found to be mutagenic in Salmonella typhimurium, Escherichia coli or Serratia marcescens, regardless of the presence or absence of mammalian S-9 liver preparations (Andersen et al., 1972; Simmon et al., 1977; Lemma and Ames, 1975; Moriya et al., 1983; Waters et al., 1982; Buselmaier et al., 1973; Fahrig, 1974). However, positive results were obtained by Shirasu (1976) and Waters et al. (1982) for Bacillus subtilis. Fahrig (1974) reported that pentachlorophenol produced a slight increase in chromosomal aberrations in cultured human lymphocytes, but there is some question as to whether the increase is statistically significant. In an in vitro study, Wyllie et al. (1975) reported that no statistically significant differences in chromosomal aberrations were seen between workers exposed to airborne pentachlorophenol (263-1887 ng/m^3) and their controls. In contrast, Bauchinger et al. (1982) observed a slight but significant increase in the number of chromosomal aberrations in the peripheral lymphocytes of workers exposed to sodium pentachlorophenol (mean blood concentration = 4.73 ± 3.41 µg/mℓ) or pentachlorophenol (mean blood concentration = 2.23 ± 1.51 µg/mℓ) with respect to controls.

4.4. WEIGHT OF EVIDENCE

Based upon the criteria for evaluating the weight of evidence of the carcinogenicity of chemicals for humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), there appear to be no data regarding the carcinogenicity of pentachlorophenol in humans, rats or mice. Pentachlorophenol is most appropriately classified in Group E - No Evidence of Carcinogenicity for Humans.

5. REGULATORY STANDARDS AND CRITERIA

The U.S. EPA (1980b) established an interim ADI of 2.1 mg/man/day for ingestion of pentachlorophenol. This was based on a NOAEL of 3 mg/kg derived from the study of Schwetz et al. (1978) on rats (discussed in Section 3.2.1.). Since the odor threshold for pentachlorophenol is lower than the interim ADI, however, the U.S. EPA (1980b) established a criterion level of 30 µg/ℓ for pentachlorophenol in water to protect the population from undersirable organoleptic characteristics.

The ACGIH (1983) has established a TLV-TWA of 0.5 mg/m³ and a STEL of 1.5 mg/m³ for occupational exposure to pentachlorophenol, with the notation that dermal absorption may contribute to overall exposure. Since chronic exposure to pentachlorophenol does not seem to produce cumulative effects, these values were chosen by analogy to similar chemicals and were intended to protect from the vascular injury seen upon acute exposure to pentachlorophenol.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Several effect levels that could be used in risk assessment were defined in Section 3.1.1. A NOAEL of 10 mg/kg bw/day based on increased liver weight was established from the study of Johnson et al. (1973), though the numbers of animals treated were not reported. NOELs of 5 mg/kg bw/day and 3 mg/kg bw/day in rats were derived from the subchronic toxicity study of Goldstein et al. (1977) and the subchronic teratogenicity study of Schwetz et al. (1978), respectively. Schwetz et al. (1974a,b) and Schwetz and Gehring (1973) reported a LOAEL of 5 mg/kg bw/day for fetotoxicity in rats exposed to pentachlorophenol during gestation. Since 3 mg/kg bw/day is the highest NOEL, which is lower than the LOAEL for fetotoxicity, this value will be used in the calculation of an AIS.

Dividing 3 mg/kg bw/day by an uncertainty factor of 100 (10 to account for the range of sensitivities in the human population; 10 for extrapolating from animals to humans) establishes an interim ADI of 0.03 mg/kg bw/day for subchronic ingestion of pentachlorophenol. Assuming that an average man weighs 70 kg, this AIS is equivalent to 2.1 mg/man/day.

6.1.2. Inhalation. The lack of pertinent data regarding subchronic inhalation of pentachlorophenol precludes quantitative assessment of risk due to exposure. It is not appropriate to derive an AIS from the TLV established by ACGIH (1983), since the value was derived by analogy to chemicals similar to pentachlorophenol.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. A NOEL of 3 mg/kg bw/day can be derived from the chronic study of Schwetz et al. (1978) on rats. Dividing 3 mg/kg bw/day by an uncertainty factor of 100 (10 for extrapolating from animals to humans; 10

to account for the range of sensitivities in the human population) establishes an AIC of 0.03 mg/kg bw/day for chronic ingestion of pentachlorophenol. Assuming that an average man weighs 70 kg, this AIC is equivalent to 2.1 mg/man/day. This value is in perfect agreement with that established by the U.S. EPA (1980b). U.S. EPA (1984) calculated a CS for the effects of fetal toxicity observed by Schwetz et al. (1978) in rats fed diets that provided 30 mg/kg/ day for 110 days of the reproductive period. The animal dose (30 mg/kg/day) was converted to a human MED by dividing by a factor of 10 to extrapolate from subchronic to chronic exposure and multiplying by 70, the assumed body weight of an average human, to express the result as mg/day. The result, 210 mg/day, corresponds to an RV_d of 2.0. The fetal toxicity observed is assigned an RV_e of 10. A CS of 20, the product of RV_d and RV_e, is calculated.

6.2.2. Inhalation. The lack of pertinent data regarding chronic inhalation of pentachlorophenol precludes quantitative assessment of risk due to exposure.

6.3. UNIT CARCINOGENIC RISK (q_1^*)

6.3.1. Oral. The carcinogenic risk associated with ingestion of pentachlorophenol cannot be quantified, since the only studies to date (BRL, 1968; Schwetz et al., 1978) have yielded negative results.

6.3.2. Inhalation. The lack of pertinent data regarding the carcinogenicity of inhaled pentachlorophenol precludes assessment of carcinogenic risk.

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APPENDIX

Summary Table for Pentachlorophenol

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS				ND	
AIC				ND	
Oral					
AIS	rat	NOEL = 3 mg/kg bw/day	none	2.1 mg/man/day	Schwetz et al., 1978
AIC	rat	NOEL = 3 mg/kg bw/day	none	2.1 mg/man/day	Schwetz et al., 1978
Maximum composite score	rat	30 mg/kg/day for 110 days of reproductive period (RV_d = 2.0)	fetal toxicity (RV_e = 10)	20	Schwetz et al., 1978; U.S. EPA, 1984

ND = Not derived